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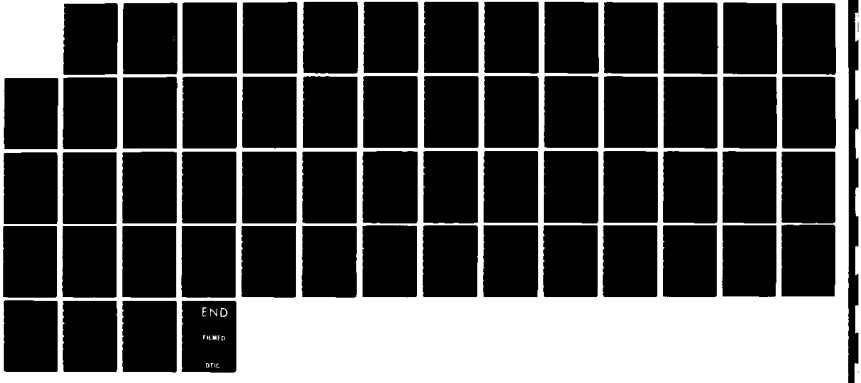

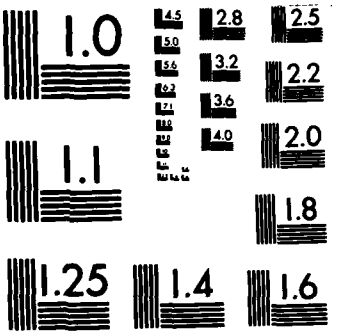

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AUTHOR: Judith Ellen McGhee

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STATEMENT(s):

AN EXPERIMENTAL TRIAL TO TEST THE EFFICACY OF TEMAZEPAM TO INDUCE SLEEP AND IMPROVE SUBSEQUENT PERFORMANCE DURING PARTIAL SLEEP DEPRIVATION AND CIRCADIAN RHYTHM DESYNCHRONOSIS

BY

JUDITH ELLEN MCGHEE, M.D.

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AN EXPERIMENTAL TRIAL TO TEST THE EFFICACY OF TEMAZEPAM TO INDUCE SLEEP AND IMPROVE SUBSEQUENT PERFORMANCE DURING PARTIAL SLEEP DEPRIVATION AND CIRCADIAN RHYTHM DESYNCHRONOSIS

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JUDITH ELLEN MCGHEE, M.D.

PROJECT PROPOSAL

Presented to the Faculty of The University of Texas

Health Science Center at Houston

School of Public Health

in Partial Fulfillment

of the Requirements

for the Degree of

MASTER OF PUBLIC HEALTH

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT HOUSTON

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Abstract

A strategy for reducing jet lag induced performance degradations by resetting circadian rhythms during prolonged rapid transmeridian flight is studied. Thirty-four aircrew member passengers on a C-141 flight were given temazepam or placebo during the flight from Oklahoma to Saudi Arabia for induction of sleep in a period compatible with the sleep cycle at the destination, but "out-of-sync" with previous patterns set at home station. Mental performance and circadian rhythm patterns were tested pre-flight, inflight and post-flight by several measurements including a computerized performance battery. The results indicated that in the temazepam group performance was improved to near baseline levels. The restorative power of temazepam induced sleep during a period of partial sleep deprivation and temazepam's ability to reset circadian rhythms prior to arrival in the new time zone were demonstrated.

Index words: Restoril, Jet Lag, Transmeridian Flight.

Preface

This proposal is written in the form of a manuscript suitable for submission to the journal: Aviation, Space and Environmental Medicine.

I would like to think the following people for their help: LtC L. Thomas, Col J. Stocks and Col R. Cowell for being my editors, reviewers, critics and friends. I would like to also thank BGen W. Kirk James for his friendship and encouragement. One of my classmates, LtC H. Gillis, deserves thanks for all of his invaluable help in the last year. The Crew Performance Branch at the School of Aerospace Medicine deserves praise for their help and encouragement to actually do my proposal. Lastly, I would like to thank the members of my committee for their help and valuable criticism. And I cannot forget my husband who put up with all of this.

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Introduction and Literature Review

The emergence of jet air travel has introduced new factors to influence the traveler's and aircrew member's health and well-being. Not only does one suffer from fatigue from the journey, but also from circadian rhythm desynchronization or jet lag.

Circadian rhythms are the approximately 24 h periodicies in physiological and psychological functions.(1) There are well documented rhythms in sleep and wakefulness, body temperature, exercise capacity, urine production and urinary excretion of certain electrolytes and corticosteroids.(1-8) Circadian rhythms have been demonstrated as well in the mental performance of tasks involving addition, auditory vigilance, decision making and reasoning.(9-14)

Circadian desynchronization due to phase shifts of rhythms at different rates in relationship to the external day/night cycle are common among travelers and aircrew. Common subjective complaints include fatigue, poor appetite and disturbed sleep patterns. There have been numerous studies on the objective changes in human functioning due to jet lag.(2,7,15-17) There is also discussion as to whether the disruption of sleep patterns or circadian desynchronosis

is the more important factor in jet lag.(18) Most authors agree that the dissociation of the staging of circadian rhythms relative to each other and to that of the new sleep/wake cycle cause the effects of jet lag as well as does sleep loss induced fatigue.

Studies among flight crews have demonstrated as many as 59-78% experience sleep disturbances after transmeridian flight.(2) These sleep disturbances may be early morning awakening, problems falling asleep and increased awakening during sleep at night.(1) Gastrointestinal disturbances such as constipation, gastritis and stomach pains are common complaints as well.(5) There are also documented decrements in performance.(1,9)

Experiments indicate a significant difference in the rate of realignment, or reentrainment, of the circadian rhythms between eastward and westward flights.(1,2,9,13,14) One review stated that 10 days for westward flights and 12 days for eastward flights are required for return to preflight performance levels.(2) Another review averaged data from 7 studies which investigated flights in both directions and presented figures for reentrainment of circadian rhythms to preflight levels. The mean rate of circadian rhythm adjustment for all variables was 57 min/day for westward flights and 92 min/day for eastward flights.(2)

Most authors have found reentrainment to be the most rapid for the first 24 h after transmeridian flight and thereafter decreasing exponentionally.(2,13,14)

There have been numerous studies on the sleep/work/rest cycles in aircrew members.(2,3,11,12,16,19,20) Sleep loss may not be as much of a problem as sleep disturbances. Thus, hypnotic drug therapy has been suggested as treatment to promote restful sleep, even when the sleep time does not correspond to the circadian need for sleep.(20)

Important criteria for a drug used for hypnotic sleep induction are several. It must be safe, effective and free of residual effects. Temazepam, a 1,4-benzodiazepine, may be a useful drug for the treatment of circadian desynchronosis and sleep induction. Certain benzodiazepines are better for this type of treatment than barbiturates, because barbiturates tend to produce residual or hangover effects and impair performance after ingestion.(20,21)

Temazepam has a short half-life in the body (5-8 h) and there are no known active metabolites formed in man.(22) A short half-life of about 6 h causes few problems with residual accumulation when the drug is given once every 24 h.(1) Temazepam has also been demonstrated to be safe and effective in formulations used in England, where doses

of 10 and 20 mg in liquid form in a soft gelatin capsule are used.(23)

There have been several performance studies done after varying doses of temazepam, since it is well known that hypnotics can adversely effect performance.(1,24) In one study after overnight ingestion of temazepam (10, 20 and 30 mg), there was no impairment of coordination at 10-16 h after administration. After morning ingestion of 20 mg temazepam, there was impairment of visuo-motor coordination at 0.5 h, which resolved by 6.5 h after ingestion.(20) A study of single doses of 5, 15 and 30 mg temazepam found only slight impairment of psychomotor performance at the 30 mg dose at 2 h after ingestion.(25) Other studies using doses of 30 mg, however, documented a trend toward impairment of visuo-motor coordination. (20,26,27) The studies suggest that at doses of 10 and 20 mg of temazepam there was no impairment in driving and other coordination skills after ingestion the previous night.(20,26,27) Reaction time, short term memory and digit substitution were also studied after ingestion of temazepam and there appeared to be no impairment 10-16 h after ingestion.(20,26,27) Therefore, temazepam appears to be a safe drug which may have little or no effects on performance 6 h after ingestion.

Other important qualities that are desirable in a hypnotic drug are that the drug shortens sleep onset latency and reduces awake activity and possibly drowsy sleep. The hypnotic should do this without effecting sleep architecture. In young adults (19 to 43 years) sleep studies were done after administration of 10 and 20 mg temazepam.(20) Total sleep time was increased and there was shortening of sleep onset latencies. The subjects reported improved sleep and well-being on the next day. This study's results have been duplicated by other researchers.(28,29) Temazepam was also studied in middle-aged men (45-55 years), but the effects were not as pronounced as in young adults even though improved sleep was reported. Temazepam also reduced awake activity and drowsy sleep when given during the day to enhance daytime sleeping.

Hypothesis

Treatment with temazepam 30 mg to induce sleep during a 25-30 h period of partial sleep deprivation and circadian rhythm desynchronization will be compared to a placebo or no treatment regimen. This period of 25-30 h was chosen because this is the usual length of time it takes for the standard deployment aircraft to leave Tinker Air Force Base, Oklahoma and reach Riyadh, Saudi Arabia. The hypothesis being tested is that temazepam has no effect on mental or

physical performance nor on physiological measurements after administration during this period of deprivation and desynchronization. The long period of partial sleep deprivation occurs because normal sleep is impossible. Due to the nature of the deployment short naps are all that is practical and possible.

Rationale Behind Study

Temazepam was successfully used by the British Royal Air Force (RAF) during the South Atlantic Campaign (the war in the Falkland Islands) to overcome fatigue and desynchronosis due to rapidly rotating shift work and jet lag. Due to the loss of sleep caused by the long air missions which often exceeded 30 h and the need to sleep in 8 h shifts, temazepam was used to ensure restful sleep and promote aircrew safety and effectiveness.(30) The usual dose was 20 mg temazepam. Temazepam was used to induce sleep at all hours of the day in young and middle-aged males. The aircrew were advised to take the dose at least 8 h before flight. However, some crews flew 6 h after ingestion without ill effects. The success of temazepam was measured by subjective fatigue reports and subjective assessments of aircrew performance and effectiveness during the missions that followed temazepam administration. The demonstrated

usefulness of temazepam makes it appear to be a useful drug to counter the effects of sleep deprivation and jet lag in other situations.

This study will investigate the usefulness of temazepam in the 552nd Airborne Warning and Control Division (Tactical Air Command) where aircrew fly long demanding missions of 14 h or longer in the potentially hazardous environment of Saudi Arabia. There are 8 time zones between the 552nd Division home base in Oklahoma and the base in Saudi Arabia. The aircrew start flying in Saudi Arabia well before the 8 to 10 days estimated as necessary for reentrainment of their circadian rhythms from United States time to Saudi Arabian time. Therefore, it can be hypothesized that they may suffer critical degradations in mental performance due to circadian desynchronosis. The objective of the study is to evaluate if temazepam is a safe and effective drug for the prevention of sleep disorders and sleep loss due to geographic displacement by jet aircraft in the setting of routine Air Force operations. The Air Force has become more aware of the fact that jet lag and sleep loss may cause serious changes in psychomotor performance. Several methods of treating or minimizing jet lag are under consideration; this is one method for treating dysfunctional sleep.

Methods and Materials

Research Design

This study will be an experimental double blind clinical trial of drug treatment for jet lag and sleep deprivation. The drug will be given to one group and a placebo will be given to the control group. The two groups will be coded as to who receives which treatment. The codes will be carried in a sealed envelope by the examiner. The examiner will have access to the codes because of safety rules onboard the United States Air Force C-141 transport aircraft. The experiment will be conducted while the subjects are passengers on a C-141 flying from Tinker Air Force Base (AFB), Oklahoma to Riyadh, Saudi Arabia (with an intermediate stop at Rhein Main Air Base, Germany). During this trip the aircrew are potentially awake for 25-30 h between the time they arise the morning of deployment until the time they arrive in Saudi Arabia and finish checking into their hotel. Temazepam will be given to induce sleep timed with regard to circadian rhythms in the aircrew during this trip. The aircrew will be allowed a 6 h time span for sleep. The period of sleep on the aircraft will coincide with the usual sleeping hours in Saudi Arabia. Therefore, the aircrew will have slept during the Saudi Arabian night cycle and will be awake and adjusted to the Saudi Arabian

day/night cycle when they land in Saudi Arabia. Otherwise, the crew would not necessarily have been able to obtain restful sleep, since this time period coincides with early afternoon and evening of their accustomed time zone (Tinker Air Force Base time).

There will be pre-flight, inflight and post-flight test periods. The dependent variables to be studied are subjective fatigue, amount of sleep obtained during the previous night and cognitive/psychomotor function (Appendix A). Some of the possible confounding variables are age, previous trips to Saudi Arabia, transmeridian travel within 12 days prior to testing and use of medications or presence of medical conditions requiring a medical waiver in order to remain on flying status (Appendix C). The independent variables are treatment with temazepam or placebo. The subjects will undergo a pre-flight test period to obtain baseline measurements and to rule out any allergic or idiosyncratic reactions to temazepam that could be hazardous to the subject if it happened in flight.

The study subjects will be stratified by the confounding variables because it is felt that these factors might effect performance, ability to sleep on the C-141 and quickness of reentrainment to the phase shift. It has been shown from shift work studies that older individuals (>40

years old) do not accomodate as well to phase changes in sleep/wake cycles as their younger counterparts. Nor do the older individuals completely adapt when they phase shift. (20) Therefore, age may influence mental performance after an 8 h phase change. There may also be an experience factor, which might be estimated by previous trips to Saudi Arabia, that might enable the subject to adjust better to time zone changes (phase changes). The aircrew may have learned by experience ways that they may reduce the stress of jet lag. If the subjects had undergone transmeridian travel within 12 days of the study then their circadian rhythms may still be in flux due to those changes and this could also influence their performance on the test. Any medical conditions requiring waivers or any medications used may also effect the aircrew's ability to cope with jet lag. The assumption would be that any pre-existing medical conditions may reduce one's ability to phase shift.

The actual measurements that will be obtained are oral temperature, numerical ratings on the Subjective Fatigue scale (Appendix D), a Sleep Survey which shows number of hours slept in the last 24 h (Appendix E), number correct on the Grammatical Reasoning test (Appendix F), number attempted on a Vertical Addition test (Appendix G) and correct performance on a computerized battery of 3

cognitive/pyschomotor tests.(13,14,35,37) The computerized battery will consist of a version of the Grammatical Reasoning test, a Pattern Recognition (Pattern Comparison) test and a Maximal Tapping test.(35) These performance tests were chosen because they require a very short practice time (<15 mins) to reach stabilization of performance due to practice effects.(35) We will consider further measurements, such as urinary and/or salivary cortisol levels, if the logistics of the sample collection and preservation can be simplified to meet the constraints of the operational setting.

The Subjective Fatigue scale is a 7 point scale developed by the Air Force School of Aerospace Medicine from a previously validated 10 point scale (SAM Form 136). The new scale (SAM Form 202) is felt to be somewhat less ambiguous and less confusing to the test subject, while still sensitive to variations in mood due to fatigue. The scale ranges from "fully alert" to "completely exhausted" with a lower number representing a more alert state. The scale has been used in studies of the effects of hypoxia and gravitational or "G" forces on performance and has been shown to be accurate in predicting performance degradations due to environmental stresses.(36)

The Sleep Survey (SAM Form 154) is used to quantitate how many hours the subject has slept in the last 24 h by 30 min intervals. There are also 3 questions at the bottom of the survey that relate to ability to sleep the previous night and whether the subject feels rested or feels the need for more sleep. In evaluating the ratings on the Subjective Fatigue scale, the analysts will attempt to correlate individual answers with the responses to the questions at the bottom of the Sleep Survey. This will be one means of cross-checking the subjects' answers to determine whether they are consistent. If a subject's reply is not consistent, i.e. the subject states s/he feels very alert when answering the Subjective Fatigue questions, but on the Sleep Survey states s/he only had 2 h of sleep, does not feel rested and feels like s/he could use more sleep, then the reliability of the subject's data is questionable. The data will need to be reevaluated to see whether they may change the group data if they are considered in the overall analysis.

The Grammatical Reasoning test, paper and pencil version, is a reasoning test that attempts to measure cognitive function and analytic reasoning associated with the brain's left cerebral hemisphere. The test presents sentences of different syntactic structure and a set of

symbols (Appendix F). The subject must determine whether the sentence describes the ordering of the symbols in the symbol set. The Grammatical Reasoning test is an attempt to measure complex mentation using a very simple test.

The Vertical Addition test is another paper and pencil cognitive test that attempts to measure number facility. This test is felt to be very sensitive to environmental stress, especially fatigue and hypoxia. The test consists of columns of 2 digit numbers in sets of three. The number of sums attempted has been shown to be a more sensitive indicator of fatigue and circadian rhythm nadirs than number of errors (31-33).

The computer battery of performance tests was developed from paper and pencil tests. The paper and pencil tests have been adapted for use on a small hand-held computer made by NEC (Nippon Electronics Company). In consultation with a psychologist from the School of Aerospace Medicine, we have chosen 3 representative tests that require approximately 7 mins to accomplish. The battery consists of the Grammatical Reasoning test, the Pattern Recognition (Pattern Comparison) test and the Maximal Tapping series. The Grammatical Reasoning test is the same as the paper and pencil version. The test is timed and the number of correct answers is stored in the computer. The Pattern Recognition test is a

visual pattern recognition and spatial memory test. The right cerebral hemisphere is the area of the brain thought to be used for this function. The test measures perceptual speed and short term memory. A pattern is randomly generated and shown on the screen. The subject has a predetermined length of time to decide whether the first pattern is the same as a second randomly selected pattern. Then the number of correct responses is recorded. The Maximal Tapping series consists of 3 timed sequences. The first sequence measures how many times the subject can tap 2 fingers of the non-preferred hand in a short amount of time. The next sequence is done with 2 fingers of the preferred hand and the last sequence is done with 1 finger from each hand in two-handed tapping. The Maximal Tapping series requires an intact corpus callosum between the cerebral hemispheres as well as an intact cortex. This is another test that is very sensitive to environmental stress.

Authorization for the study will have to be granted by the Air Force Medical Services Center/Deputy Command Surgeon (AFMSC/SGP). Also the experiment will have to be approved by a military Protection of Human Subjects committee. The proposal will have to assure the committee and the Deputy Surgeon that confidentiality will be maintained, that the subjects give informed consent and that the drug therapy

will not be harmful in any way. All information on the subjects will be handled in a coded form with no names used. An Air Force consent form (Appendix B) will be used that explains the risks and benefits of temazepam therapy, the possibility that the subject might receive a placebo, assurances that any information obtained in this study will not be used against them in any way and that they may drop out at any time without prejudice. Once this is done then the study will have to be approved by the Tactical Air/Command Surgeon (TAC/SG) who is responsible for the health of the 552nd Airborne Warning and Control Division (AWACD) aircrew member.

Aircrew members are not allowed to take any drugs while they are on flying status, so they will have to be temporarily placed in a Duty Not to Involve Flying (DNIF) status while they are taking the drugs. However, this should not result in any lost time to the Air Force since the aircrew member is not actively flying while they are passengers on the C-141. Also, during the pretest session the aircrew member has already been removed from the active flying roster until they report for duty in Saudi Arabia 24 h after they arrive. This allows ample time for temazepam to be eliminated from their systems.

Population of Study

The study group will be defined as active duty U.S.A.F. aircrew members assigned to the 552nd AWACD stationed at Tinker AFB, Oklahoma, currently on flying status and available for duty in Saudia Arabia. There are 1907 personnel on flying status assigned to the Division. They each have a relatively equal and random risk of being sent to Saudia Arabia for a 3 week tour of duty. Everyone in the Division goes to Saudia Arabia. Some personnel go more times per year than others; at any one time everyone has a risk of being sent to Saudia Arabia. The study sample will be drawn from the passenger manifest of the weekly C-141 flight which goes to Saudia Arabia.

The sample group will consist of 34 aircrew members, 17 of which will receive temazepam and 17 of which will receive placebo. The sample size of 34 was picked because there are always 2 crews, of 17 each, going to Saudia Arabia on the C-141. The crew positions on each crew are the same with similar rank structures for each crew position. The crew positions also will have a similar range of ages.

Sampling Design

The overall personnel selection will be a haphazard sample, since the crew members already in Saudia Arabia

cannot be included in the study. However, the crews will be picked randomly from the haphazard sample. The 2 crews will be picked randomly from a passenger manifest that will also be picked at random from the month in which the study will be conducted. The passenger manifests are made up approximately 1 month before departure. Last minute changes are usually held to a minimum because of the difficulty in getting visas for entry into the country. Each crew member will be allocated randomly to either the temazepam or placebo group. The sample size of 34 is fixed because that is the minimum number of aircrew members that always go to Saudi Arabia. Due to operational constraints that number cannot be readily increased. Whether this is a large enough sample size cannot be totally determined until the data have been analyzed to see what the power will be for detecting differences due to treatment differences. The optimal sample size will also be a function of the varability of the data sets.

The subjects will be randomized to 9 temazepam and 8 placebo subjects for one crew of 17, with the reverse on the other crew. This will be done to try to minimize "crew effects" or variances in the intragroup mean performance scores due to group effects. It will also tend to minimize differences if one crew is assigned to night flights and one

crew is assigned to day flights during the observational period in Saudi Arabia.

Data Collection

The subjects will collect data and be tested over 11 days: 2 days pre-flight, 2 days inflight and 7 days post-flight. Data that will be collected throughout the 11 days are the sleep survey every 24 h and the Subjective Fatigue scale and oral temperature every 4 h (using clinical thermometers). Individual logbooks consisting of Sleep Survey sheets and Subjective Fatigue sheets will be handed out to every subject. The subjects will write their oral temperatures in degrees Fahrenheit $\pm$ 0.1 on the bottom of the Fatigue scale. The subjects will be identified by a code number consisting of the last 4 digits of their security number.

On day 1 (preflight) at Tinker Air Force Base, Oklahoma, everyone will fill out a short demographic questionnaire, an informed consent form and a Sleep Survey. They will then take the Vertical Addition and Grammatical Reasoning tests and fill out the Subjective Fatigue scale. The Vertical Addition and Grammatical Reasoning tests will be given 2 more times at 4 h intervals from the first administration in order to establish time qualified

references. This will allow us to measure test performance variations due to the time of day when the test is given. We will then compare the test values for the post-flight tests to those obtained on the tests given pre-flight that were given at approximately the same time of day (pre-flight). This is an attempt to lessen the effects that time of day has on performance testing from causing variations in our post-flight test values. Everyone will also begin taking their oral temperatures every 4 h. Also 25 test subjects will be randomly selected to take the computerized battery. The number 25 was chosen based on being able to use 5 computers during the time span alloted. Everyone will then be given a logbook to take home. Then the subjects will be given the pills, either placebo or temazepam (controlled in a random double blind fashion). The subjects will take the pills that night near normal sleep times. This will be considered the ground test portion of the drugs. The subjects will then be interviewed the next day so that any adverse reactions can be reported promptly.

Day 2 will be spent in unscheduled activity, getting ready to leave the next day. The subjects will continue the Sleep Survey, Fatigue scale and oral temperature measurements.

Day 3 is the beginning of the flight period. The schedule is approximately as follows.

Tinker AFB, USA time	Saudi time
0500 Wakeup, Day 3	1300 Day 3
0700 Showtime Tinker	1500
1000 Takeoff Tinker	1800
2000 Land Germany	0400 Day 4
2300 Takeoff Germany	0700
0600 Land Saudi, Day 4	1400
0900 Arrival at hotel	1700

The computerized battery will be administered to the same 25 subjects who had previously taken it immediately after takeoff from Tinker AFB. Temazepam and placebo will be administered approximately 3 h into the flight or at about 1300h Tinker time (2100h Saudi time). The subjects will attempt to sleep for 6 h. The computer battery will be administered again when the subjects are awakened about 1 h prior to landing in Germany. The computer tests will be given again about 30 mins after takeoff from Germany and again about 1 h prior to landing in Saudi Arabia. The subjects will continue the Sleep Survey, Fatigue scale and oral temperature measurements inflight. Temazepam and placebo will not be given again.

Day 4 is the end of the flight period which terminates in Riyadh, Saudi Arabia. Approximately 2-3 h post-flight, after the Customs inspection is finished, the subjects will arrive at the hotel. The Vertical Addition and paper Grammatical Reasoning tests will be given again to everyone. The same 25 subjects will again complete the computer battery. The time of administration of these tests will be noted so that we can compare these results to the test results from the pre-flight tests which were obtained during the same time of day. This will help us reduce some of the score variability due to administration at different times during the circadian cycle.

During days 5 through 11 the 34 subjects will continue to fill out their log books for the Sleep Survey, Fatigue scale and oral temperature. The subjects will have approximately 48 h downtime after their arrival in Riyadh during which they are not scheduled for any flying duties. After this downtime, the crews will start flying the routine E-3A missions in Saudi Arabia. The exact duty/sleep schedules are classified at this time. The logbooks will be collected on Day 11 prior to the examiner's return to Tinker.

Degree of Reliability and Validity of Measurement

Oral temperature and number of sums attempted in the Vertical Addition test have been determined to be very reliable and valid measures of circadian rhythm and mental performance in several studies.(31-34) There is strong correlation between the 2 measures. In a series of 3 experiments, the correlation between oral temperature and sums attempted was positive with similiar relationships between the measurements for each subject.(31-33) Therefore, the correlation appears to be reproducible and consistent between studies. The standardized Fatigue scale has also been shown to be well correlated with objective measures of fatigue by previous use in other School of Aerospace Medicine studies of fatigue. Statistical significance will be assumed on the tests for a p value of <0.10.

The psychomotor performance tests, such as Grammatical Reasoning, have undergone extensive development by both the civilian sector and a Tri-service military performance testing group (Unified Tri-service Cognitive Performance Assessment Battery). The tests were analyzed for stability of means (average scores of the tests) and reliability of test scores. The tests have been subjected to repeated measures analysis of variance and covariance. The

conclusion reached by both test groups is that for these performance tests one is able to achieve psychometric stability of the measures of performance. The psychomotor tests have been used in a variety of test situations to determine the effects different environmental stressors, such as hypoxia and fatigue, have on operator performance in high performance aircraft.(35)

Analysis of Data

The data will be analyzed for each test and the scores will be transferred to computer punch cards. Mean scores for each treatment group will be calculated. The hours slept per 24 h period on the Sleep Survey will also be entered for each subject and also analyzed for treatment group differences. The data will be kept in 2 forms for each test measurement, one form of data will be individual scores and the other form will be group mean scores.

One relationship to be examined is how many days it takes for the oral temperature to synchronize with the Saudi Arabian sleep/wake cycle. This data analysis will be performed on results stratified by age, previous trips, trip within the last 12 days and medication and/or medical waiver for placebo and temazepam subjects (Appendix H). Another relationship to be studied is whether subjective fatigue was

reduced in stratified subjects for placebo and temazepam groups. The number of hours slept as recorded on the Sleep Survey will be compared to the ratings on the Fatigue scale for each stratification for the temazepam and placebo groups. Then the mean scores on performance tests will be analyzed for each stratification for the 2 treatment groups.

The observations will be analyzed by using the 2 way analysis of variance method.(Appendix A) The null hypothesis that we wish to test is that there are no differences on any of the measures between the 2 treatment group populations. We wish to find out whether there is significantly more variation between the treatment groups than within the groups. As the standard for comparison we will use the pooled variation within the treatment groups. There should be an observational variability within the treatment groups. Therefore, to be statistically significant there should be a large difference in variance between the treatment groups as compared to the within the group variance. The row and column effects of each dependent variable will be analyzed.(Appendix A) An F statistic will be generated for each set of variables. Then a p value will be obtained. The final analysis should show that there is a statistically significant difference for each dependent variable between the 2 treatment groups. The data will also

be analyzed to see whether further variance analysis should be done. After scrutinizing the data we may decide that there are more factors that influence performance, such as "crew effects", than we have originially considered in our analysis of variance. However, we cannot determine whether we will need to do an extended variant analysis until the data have been collected and examined.

If during our examination of the data we find that we do not have a complete set of data on one subject, such as a missing temperature, then we will exclude that individual from the analysis of that dependent variable.

Results

The performance test battery should measure accurately the between subject variations, as well as between treatment group variations. The battery should also be able to overcome some sample size problems, due to the high power from replications and the maximized test-retest reliability. The performance tests used in this study are some of the tests that have been developed by the Armed Forces for human performance investigations of environmental effects using repeated measures.(35) The investigator in human performance studies needs tests which remain stable during repeated measurements. Stability is essential since the

tests will be used for testing before, during and after environmental exposure.

Using the performance test results as a guide, we should be able to get very sensitive indications of the effects of fatigue on human performance capabilities. If the subjects respond truthfully on the Fatigue scale, instead of overcompensating and answering how they think the investigator wants them to answer, we should see definite correlations between fatigue states and performance. There is one caveat, however. In any highly motivated group, the subjects will attempt to compensate to a degree for the performance degradations due to fatigue and lack of sleep. The design of this study should tend to offset this effect. Subjects have been shown to be able to compensate for sleep loss up to 24 h in length without large changes in their performance.(6) However, a 30 h sleep deprivation period combined with a large transmeridian phase shift will tend to overcome the subjects' ability to compensate. This has been demonstrated before in other studies of sleep loss and performance.(2)

The unique aspect of this study is the use of temazepam in an operational setting. Results showing that temazepam induced sleep can offset the effects of jet lag will be very important to consider for its future use in the operational

missions of the Air Force. Our results showing definite differences between the temazepam and placebo groups will have to be analyzed in great detail to try to insure as conclusively as possible that are results are real.

We are anticipating statistcially significant differences between the 2 groups because of the restorative power of sleep, even drug induced sleep. We feel that there will be a definite improvement in mental performance post-phase shift. This will be due to the temazepam induced sleep markedly reducing the consequences of an 8 h time zone change and 30 h sleep deprivation. Due to the nature of flight aboard a C-141, it is difficult for anyone to get restful sleep. The environment is too cold or too hot, very noisy and subjects the passenger to all types of vibrational forces. Also if you do go to sleep, it is either while you are sitting upright in a cramped seat or stretched out on top of the cargo or on the freezing floor. Sleep is possible but usually the aircrew member naps and does not sleep for more than 1 h at a time.

Conclusions

If we are able to demonstrate conclusively the restorative power of hypnotic drug induced sleep to overcome rapid phase shifts and sleep deprivation, we have

demonstrated a very important strategy. This strategy will allow the Air Force to better ensure good performance in highly stressful situations after a standard transmeridian deployment. The results of our study should be very valuable in planning strategic missions of long duration. We will have demonstrated a safe, easy and effective strategy to insure that the aircrew is ready to "Fly and Fight", no matter how far away from home they are or how long it took them to get there.

Circadian rhythms and jet lag have been investigated by many experimenters in many different ways. We think that this study contributes something unique to the field. We will have done an experimental clinical trial in an operational setting. We will not have altered the routine deployment environment in any way. We have merely tried to develop a stratagem to deal with it successfully.

Appendix A

Example of Data Tables - 2 way analysis of variance

Mean No. of Sums Attempted	Age	
	<40yo	>40yo
Placebo grp		
Temazepam grp		

Appendix B

Sample Consent Form (AFR 169-3)

I, _____, having full capacity to consent, do hereby volunteer to participate in a research study entitled: An experimental clinical trial to treat Jet Lag with Temazepam under the direction of Dr. Judith E. McGhee. The implications of my voluntary participation; the nature, duration and purpose; the means and methods by which it is to be conducted; and the inconveniences and hazards which may reasonably be expected have been explained to me by Dr. McGhee, and are set forth on the reverse side of this Agreement, which I have initialed. I have been given an opportunity to ask questions concerning this research project, and any such questions have been answered to my full and complete satisfaction. I understand that I may at any time during the course of this project revoke my consent, and withdraw from the project without prejudice; however, I may be required to undergo certain further examinations, if in the opinion of the attending physician, such examinations are necessary for my health and well-being.

_____

signature date

I was present during the explanation referred to above, as well as the volunteer's opportunity for questions, and hereby witness the signature.

_____

signature date

Explanation of Research Project

1. The subject will be given pills 2 times during the project. The pills will either be temazepam 30mg (Restoril) or a placebo (sugar pill). Temazepam is a sleeping pill given to people who are having trouble sleeping or who want to sleep at a time they do not usually go to sleep and need help falling asleep. The sugar pill is a pill made out of sugar that looks like the sleeping pill; so that you do not know which pill was given to you, placebo or temazepam.

2. The subject will participate in the study for 11 days. The project will start 2 days before a routine deployment to Saudi Arabia and continue for 7 days after arrival in Riyadh.

3. The subject will be required to take his/her own temperature with an oral thermometer every 4 h during the testing period. The subjects will also have to fill out a form that rates how fatigued or tired you are and a form that shows how many hours you slept the night before. Two times during the testing period the subject will have to do some paper and pencil tests. One test is made up of simple addition problems. The second test is short sentences that must be read, understood and answered. The latter is a very simple grammar or English test.

3. Some of you, 25 of the original 34, will be picked out by chance and will do a short series of 3 tests on a hand held computer. You will do the simple grammar test, a test that shows you 2 patterns and asks you if they are alike and a test that measures how fast you can tap your fingers. As a reward for doing the computer tests you will get to play a missle command game. All the tests are timed, but you should be able to answer most of the questions.

4. We are doing this project so that we can test new ways to make long deployment flights less difficult for the passengers. We want to find a way to lessen the effects of no sleep and an uncomfortable flight on a C-141 on your mental performance and well-being. The Air Force is interested in trying to improve your ability to perform after long periods of little or no sleep, especially when you have to cross several time zones.

5. This project has not been done in exactly this way before. The sleeping pill, temazepam, has been studied a lot by other scientists, especially the British. All of the studies done on temazepam have shown that it helps people to sleep better and makes them feel better when they wake up. The British Royal Air Force used temazepam during the war in the Falkland Islands, so that their aircrew could get some sleep at odd times of the day or even when they only had an 8 h period for crew rest. The British have not reported any

problems with the use of this drug. However, so that we can try to keep from influencing the results of the performance tests we are going to give some of you sugar pills and some of you temazepam. We will keep a secret code of who gets what by using the last 4 numbers of your social security number as your code number.

6. There are some risks associated with taking any medication. The manufacturer of temazepam has published the risk of side effects that they found in their studies. If you are pregnant there is a chance that your baby may be harmed if you take this drug. Therefore, if you are pregnant you cannot do this study. You should not drink alcohol within at least 6 h of taking temazepam. There is a risk that the two together will cause confusion, dizziness and interfere with your ability to function. You also have to be careful if you take temazepam and try to drive or operate heavy machinery right after you have taken the drug. You might have an accident, so you should wait until the drug has worn off. Also if your liver or kidneys are diseased, temazepam might make them worse. Here is a list of the adverse reactions found by the manufacturer. In 795 people who took the drug: 17% had problems with drowsiness, 7% had problems with dizziness and 5% had problems with lethargy or decreased energy. Other side effects were: confusion, a "high" feeling and a relaxed feeling (2-3%).

Much less common were weakness, decreased appetite and diarrhea (1-2%). Rarely reported were tremor or shakes, poor concentration, poor equilibrium or unsteadiness, falling and heart palpitations (less than 1%). Temazepam can be addictive or habit forming if taken in large doses over long periods of time.

The sugar pill or placebo has no known side effects.

8. We will do our best to keep the risk of side effects as small as we can. If anyone has taken temazepam before and is allergic to it or has problems when they take it, they will not be in the study. Everyone's medical records who participate in the study will be screened by a Flight Surgeon to make sure there is no reason that they cannot participate in the study. On Day 1, 2 days prior to the deployment, we will give you either temazepam or the sugar pill. We will explain how you should take the pills and what symptoms or problems you should be looking for. A Flight Surgeon will be available by phone or in person to talk to, if you think that you are having problems. If you have problems we will examine you to make sure you are alright, then we will drop you from the study. We are pretesting or groundtesting the drugs before you fly to make sure you can take the pills without problems.

9. You may derive some benefit from this study. After you have been tested with the temazepam and the study has ended, you may be able to take it again in the future if you want to sleep on the C-141 to Saudi Arabia. You will have to discuss this with your local Flight Surgeon, but usually you can take a sleeping pill again once you have been ground tested. If our study is accepted by Tactical Air Command and the Air Force Surgeon General's office, we hope to have temazepam used routinely on long deployments, for sleeping at odd hours of the day due to mission requirements and in any way the Surgeon General thinks that it would benefit the flying population.

10. If at any time you want to drop out of the study, you can. You will not be penalized in any way. All of the study information will be coded under the last 4 digits of your social security number. Only the main examiner, Dr. McGhee, will have access to a key that shows whose name goes with what number. None of the study results can be used in any way against you. Your participation is entirely voluntary. No information on anyone will be given out to anyone except the people directly involved in the study who have a need to know. You certainly have the option not to participate in the study and to try to sleep on your own on the C-141 without drugs. If you feel that any of this information is not clear, please feel free to ask Dr. McGhee

to explain it to you. We want your cooperation and we want you to understand what is going on at all times. A Flight Surgeon involved with the project will be accompanying you to Riyadh, so that we can insure that your health is protected.

Appendix C

Demographic Questionnaire

Name _____

Social Security Number _____

Rank _____

Crew Position/DAFSC _____

Age _____

Sex _____

Race (White/Black/Other) _____

Marital Status (Married/Single/Divorced) _____

Any Children? (Yes/No) _____

Could you possibly be pregnant? (Yes/No) _____

Have you taken temazepam before? (Yes/No) _____

Any previous trips to Saudi Arabia? (Yes/No) _____

Any trips crossing more than one time zone within the last 12 days? (Yes/No/When?) _____

Are you on any medical waivers so that you may stay on Flying Status? If yes, for what? _____

_____

Are you taking any medications? If yes, what and why?

_____

_____

Appendix D

Subjective Fatigue Scale

NAME	DATE AND TIME

SUBJECTIVE FATIGUE

(Circle the number of the statement which describes how you feel RIGHT NOW.)

1	Fully Alert; Wide Awake; Extremely Peppy
2	Very Lively; Responsive, But Not At Peak
3	Okay; Somewhat Fresh
4	A Little Tired; Less Than Fresh
5	Moderately Tired; Let Down
6	Extremely Tired; Very Difficult to Concentrate
7	Completely Exhausted; Unable to Function Effectively; Ready to Drop

COMMENTS

Oral Temperature---_____

WORKLOAD ESTIMATE

(Circle the number of the statement which best describes the MAXIMUM workload you experienced during the past work period. Put an X over the number of the statement which best describes the AVERAGE workload you experienced during the past work period.)

1	Nothing to do; No System Demands
2	Little to do; Minimum System Demands
3	Active Involvement Required, But Easy to Keep Up
4	Challenging, But Manageable
5	Extremely Busy; Barely Able to Keep Up
6	Too Much to do; Overloaded; Postponing Some Tasks
7	Unmanageable; Potentially Dangerous; Unacceptable

COMMENTS

PREVIOUS EDITION WILL BE USED

SAM FORM 202 APR 81 — CREW STATUS SURVEY

Appendix E

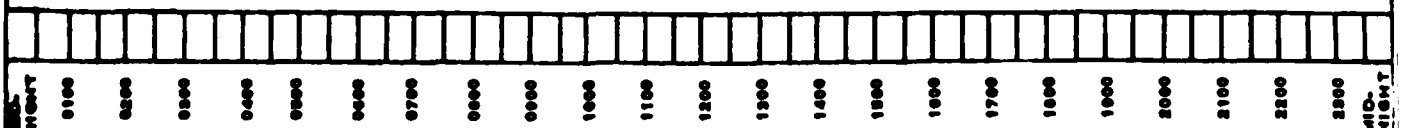
Sleep Survey

SLEEP SURVEY

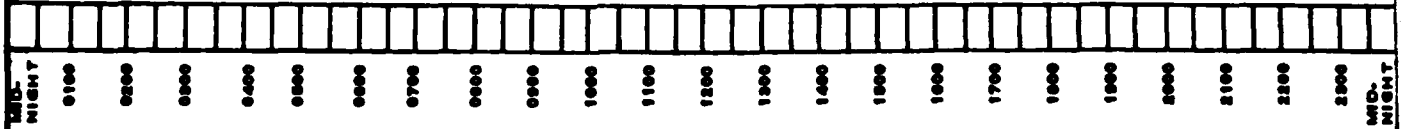
NAME (Last, First, MI)	GRADE	DATE/TIME

1. On the chart below, mark an X in each half hour interval you slept yesterday and today.

YESTERDAY



TODAY



2. HOW MUCH TROUBLE DID YOU HAVE GOING TO SLEEP LAST NIGHT?

☐ NONE ☐ SLIGHT ☐ MODERATE ☐ CONSIDERABLE

3. HOW RESTED DO YOU FEEL?

☐ WELL RESTED ☐ MODERATELY RESTED ☐ SLIGHTLY RESTED ☐ NOT AT ALL

4. DO YOU FEEL LIKE YOU COULD HAVE USED SOME MORE SLEEP?

☐ YES ☐ NO

SAM FORM 154 SEP 76 PREVIOUS EDITION WILL BE USED REMARKS ON REVERSE

NAVAL AEROSPACE MEDICAL RESEARCH LAB
BOX 29407
MICHOUD STATION
NEW ORLEANS LOUISIANA 70189

By G.E.I. INC.
FOR
HUMAN FACTORS DIVISION

SSN: DATE/TIME:

THIS IS A TEST TO SEE HOW QUICKLY AND ACCURATELY YOU CAN UNDERSTAND COMPLEX STATEMENTS. IT IS NOT EXPECTED THAT YOU WILL FINISH ALL THE PROBLEMS IN THE TIME ALLOWED.

YOU ARE TO PLACE A SLASH THROUGH THE CORRECT ANSWER, T OR F, DEPENDING ON WHETHER EACH STATEMENT IS TRUE OR FALSE. SEVERAL PRACTICE PROBLEMS ARE GIVEN, AND THE FIRST TWO ARE CORRECTLY WORKED FOR YOU.

THIS PRACTICE MAY HELP YOUR SCORE.

PRACTICE PROBLEMS:

1.	A FOLLOWS B ----------	[BA]	/	F
2.	B PRECEDES A ----------	[AB]	T	/
3.	A IS FOLLOWED BY B ---	[AB]	T	F
4.	B IS NOT FOLLOWED BY A	[BA]	T	F
5.	B IS PRECEDED BY A ---	[BA]	T	F
6.	A DOES NOT PRECEDE B -	[BA]	T	F

YOUR SCORE ON THIS TEST WILL BE THE NUMBER OF PROBLEMS ANSWERED CORRECTLY.

DO NOT TURN THIS PAGE UNTIL YOU ARE ASKED TO DO SO.

Appendix G

INSTRUCTIONS

(NF)

In this test you work addition problems. Add up the figures and write your answers in the boxes below the problems.

The first problem has been worked correctly. Practice on the others.

2	77	6	30	67	3	6	70	33	13
10	21	56	74	47	34	38	74	25	51
47	63	7	6	68	72	95	82	91	83
59									
22	32	25	16	63	4	79	5	59	99
76	15	10	20	37	55	6	86	27	78
22	32	90	88	35	47	73	13	18	70

When the signal is given, please turn the page and work as many addition problems as you can. Work fast.

35	24	10	16	20	33	32	51	26	38
38	23	16	86	38	42	38	97	1	50
31	96	25	91	47	96	44	33	49	13
66	67	40	67	14	64	5	71	95	86
14	90	84	45	11	75	73	88	5	90
68	5	51	18	20	33	96	2	74	19
20	46	78	73	90	97	51	40	14	2
64	19	58	97	79	15	6	15	93	20
5	26	93	70	60	22	35	85	15	13
7	97	10	88	23	9	98	42	99	64
68	71	86	85	85	54	87	66	47	54
14	65	52	68	74	87	37	78	22	41
17	53	77	58	71	71	59	36	50	72
90	26	59	21	19	23	41	61	33	12
41	23	52	55	99	31	52	23	69	96
26	99	61	65	53	58	4	49	80	70
46	98	63	71	62	33	26	16	7	45
42	53	32	37	32	27	7	36	51	80
32	90	79	78	53	13	55	38	58	59
5	3	72	93	15	57	12	10	14	21
31	62	43	90	90	6	18	44	32	53
17	37	93	23	78	87	35	20	96	43
77	4	74	47	67	21	76	33	50	25
98	10	50	71	74	12	86	73	58	7
52	42	7	44	38	15	51	29	12	42
49	17	46	9	62	90	52	84	77	27
79	83	86	19	62	6	76	50	3	10

Subject _____ Examiner _____ Date _____

Appendix H

Graph of Values

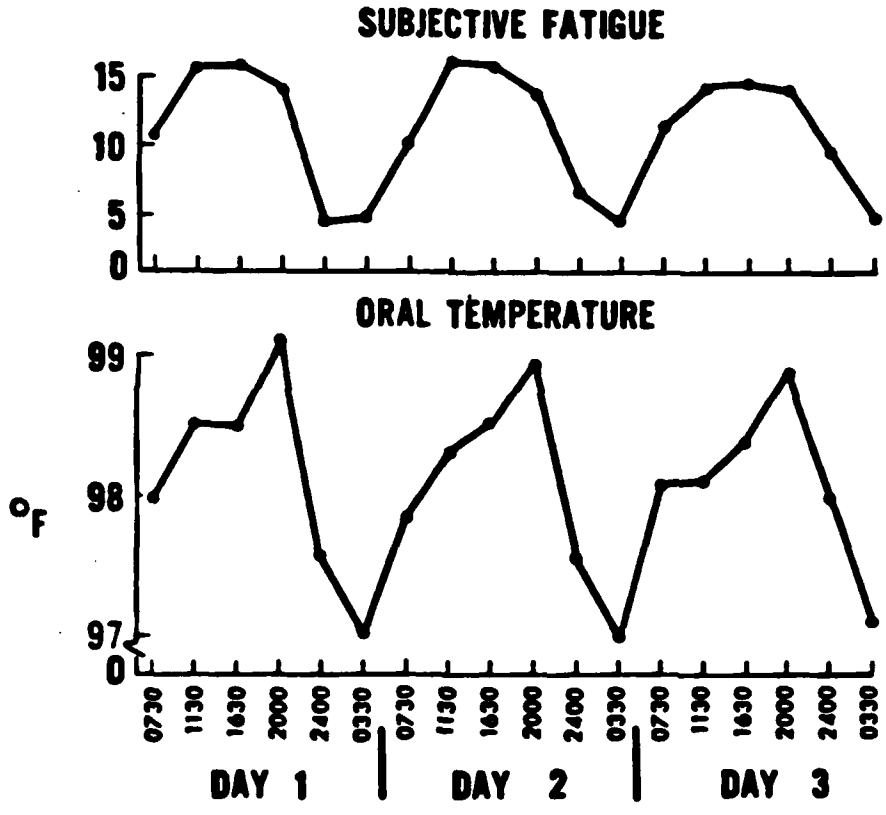


Figure 2. Typical circadian patterns for oral temperature and self ratings of subjective fatigue. (37)

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VITA

Judith Ellen McGhee was born at Sampson Air Force Base, New York, on September 12, 1954, the daughter of then Captain Gail Kincaid McGhee and Alice Nichols McGhee. After completing Casady School, Oklahoma City, Oklahoma in 1972, she entered Mills College, at Oakland California. She received her Bachelor of Arts degree with a major in Chemistry from Mills College in May 1976. She graduated from the University of Oklahoma College of Medicine and was awarded a Doctor of Medicine degree in June 1980. She completed an Internship in Family Practice in June 1980. She successfully completed the Aeromedical Primary course for Flight Surgeons in September 1981 and was awarded her wings. She was then assigned to the 963rd Airborne Warning and Control Squadron (AWACS) of the 552nd AWACD, Tactical Air Command. In December 1981, she was made Chief of Flight Medicine, United States Air Force Hospital, Tinker Air Force Base, Oklahoma. In May 1983, she was selected Command Flight Surgeon of the Year for 1982 for Tactical Air Command. She is presently in the Residency in Aerospace Medicine, Brooks Air Force Base, Texas. In 1978, she married William Lee Dennis of Oklahoma City, Oklahoma.

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